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Original Research Article

HPV and Oropharyngeal Carcinoma - A Histomorphological Analysis

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Abstract:

Introduction: HPV associated oropharyngeal carcinomas are of great importance nowadays because of its differing behavior irrespective of the tumor differentiation. The aim of this study is to analyse the incidence of HPV associated oropharyngeal carcinoma in our institute and various histomorphological features associated with these tumors.

Materials and Methods: This is a retrospective study conducted in Department of Pathology, Thanjavur Medical College. All cases of oropharyngeal squamous cell carcinoma which meets the inclusion and exclusion criteria during 1year study period were included. The clinical parameters were retrieved and histomorphological features were analysed in H&E stained sections. Immunohistochemical analysis of p16marker was done and compared with the clinical and histopathological details.

Results: Of the 50 cases included in the study, 80% occur in male and 44% occur in tonsil and tonsillar fossa. 60% cases are keratinizing SCC and 34% cases have good lymphocytic response. P16 positivity is seen in 46% cases. 60.9% cases of HPV positive tumors are nonkeratinising. Lymphocytic response is present more in HPV positive tumors compared to HPV negative tumors. All HPV associated tumors have low Worst pattern of invasion.

Discussion and Conclusion: HPV associated tumors are most common in the oropharynx and they have better prognosis with increased response to therapy. HPV positive tumors are more common in tonsil because it is the easily accessible lymphoepitheial site for the entry of organism and they exhibit greater CD8 positive T cell infiltrate. Our study also showed statistically significant association between good Tumor infiltrating lymphocytes, absence of keratin and HPV positivity. In conclusion HPV positive tumors are associated with better pathologic prognostic factors.

Keywords: Human papillomavirus, Oropharyngeal carcinoma, histology.

Introduction

The oropharynx is the area behind the oral cavity which includes posterior third of tongue, soft palate, pharyngeal wall and spaces like glossotonsillar sulci, valleculae, oropharyngeal isthmus.[1] The most common malignancy occurring in this area is Squamous cell carcinoma which accounts for 90-95% of all malignancies. The incidence of Squamous cell carcinoma has been increasing every year since mid2000s mostly because of rise in carcinomas linked with HPV.[2] The HPV positive carcinomas tend to act differently and have better prognosis than HPV negative carcinoma.[3]

The aim of this study is to find the incidence of HPV positive oropharyngeal SCC in a tertiary care center and to analyse the various histomorphological parameters observed in HPV positive SCCs.

Materials and Methods

This is a retrospective study conducted for a period of 1 year in a tertiary care hospital in South Tamilnadu. All cases reported as oropharyngeal squamous cell carcinoma during this period were included in the study. Non-squamous cell carcinomas and sarcomas were excluded. The clinical details like age, sex, laterality, site and stage were collected. Paraffin blocks of the included cases were retrieved. The hematoxylin and eosin stained slides were analysed for type of tumor, grade, and presence of keratin, lymphocytic immune response (tumor infiltrating lymphocytes) and worst pattern of invasion. Unstained slides of selected cases were subjected for Immunohistochemical expression of P16 which is a marker for HPV infection. Nuclear expression with intensity of 2+/3+ in more than 75% of cells or

more than 50% positive cells with more than 25% confluence is taken as positive.[4] All the parameters were entered in excel sheet and statistical analysis was done using SPSS software.

Results

A total of 53 cases of oropharyngeal squamous cell carcinoma (OPSCC) have been reported in our hospital during this study period. Among these, 3 cases have been excluded due to various reasons like nonavailability of blocks, inadequate material for IHC. Remaining 50 cases were analysed based on clinical details, histological parameters and subjected for IHC marker P16.

Table 1: Correlation of Clinicopathological Pathological parameters with p16 expression in Oropharyngeal carcinomas

Variable	Category	P16 (+VE)	P16 (- VE)	P value
Site	Post tongue	5(21.7%)	14(51.9%)	0.08
	Tonsil	12(52.1%)	10(37.0%)	
	Soft palate	2(8.7%)	2(7.4%)	
	Vallecula	3(13%)	1(3.7%)	
	Pharyngeal wall	1(4.3%)	0(0%)	
Grade	1	9(39.1%)	13(48.1%)	0.522
	2	14(60.9%)	14(51.9%)	
Stage	II	5(21.7%)	7(25.9%)	0.71
	III	12(52.2%)	11(40.7%)	
	IV	6(26.1%)	9(33.3%)	
TIL	High	12(52.2%)	5(18.5%)	*0.012
	Low	11(47.8%)	22(81.5%)	
Keratin	absent	14(60.9%)	6(22.2%)	*0.005
	present	9(39.1%)	21(77.8%)	
WPOI	Low	23(100%)	25(92.6%)	0.493
	high	0(0%)	2(7.4%)	

***significant p value**

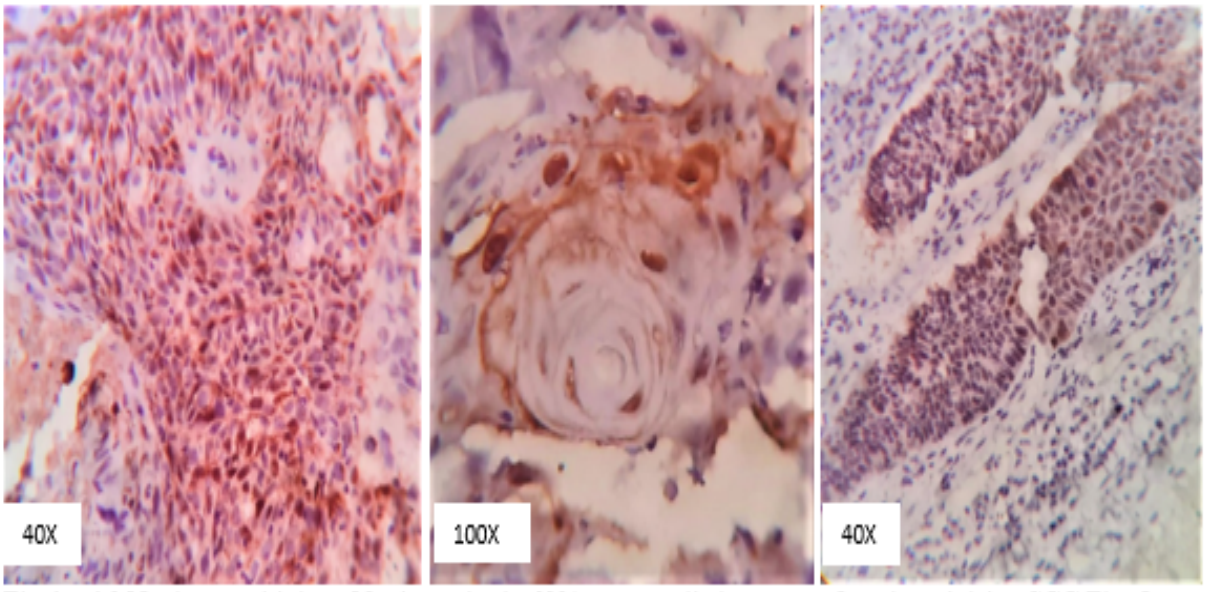

Figure 1: p16-Nuclear positivity of 3+ intensity in 60% tumor cells in a case of nonkeratinising SCC. Fig-2- nuclear positivity of p16 observed in a case of keratinizing SCC. Fig-3-- Nuclear positivity of p16 with 2+ intensity in nonkeratinising SCC

Based on the clinical data, 80% of the cases were males. The mean age of occurrence of OPSCC was 61years. Most of the cases occurred in the tonsil and tonsillar fossa (44%) followed by posterior third of tongue (38%). Pharyngeal wall constituted the least common site (2%). On analyzing the stage at presentation it was observed that 46% cases present at stage III and 30% cases present at stage IV. Histopathologically good lymphocytic immune response was observed in 34% of cases. 60% of cases had either intra or extracellular keratin. With IHC, P16 positivity was seen in 46% of the cases of

which 3+ intensity was seen only in 2% cases. (Table-1) Collectively it was observed that HPV associated OPSCC was more common in tonsil (52.1%) whereas non HPV associated OPSCC was more common in posterior third of tongue (51.9%). No significant association has been made between HPV infection and grade of tumor. Lymphocytic immune response was seen more in HPV associated OPSCC and was rarely seen in HPV negative OPSCC.

Nearly 81% of HPV negative tumors do not have tumor infiltrating lymphocytes. This correlation is statistically significant with p value of 0.005. This indicates when we see tumor infiltrating lymphocyte, it has 4times increased possibility of HPV associated.60.9% cases of HPV associated tumors were nonkeratinising SCC whereas 77.8% cases of HPV negative cases were Keratinising SCC. When Worst pattern of invasion (WPOI) was analysed, all 1 00% cases of HPV associated OPSCC have low WPOI (pattern 1-3).

Discussion

The AJCC staging system has defined HPV positive and HPV negative OPSCC as separate entities because they have distinct molecular profile, tumor characteristics and outcome.[5] The HPV associated cancers are most common in the Oropharynx.[6,7] HPV associated OPSCC are of great importance nowadays because of its differing behavior and response to therapy when compared to HPV negative cases. HPV positive cases show better prognosis and increased response to treatment. [8] In many studies the characterization of HPV in head and neck cancer was done by PCR and Immunohistochemistry which detect the P16INK4A cell protein expression. [9,10]

In high risk HPV infection the viral E7 protein inactivate the cellular Rb protein which results in upregulation of various proteins associated with cell cycle including p16 which is an indirect surrogate marker for human papillomavirus infection. The sensitive and specific test for identifying HPV is PCR and QRT-PCR. But due to low cost and sensitivity, p16 immunohistochemistry is commonly used as a complementary procedure to detect HPV infection.[10] College of American pathologist guidelines suggest to perform p16 as an initial test to detect HPV. [11]

Hence we performed p16 IHC to characterize HPV infection and we analysed the histopathological parameters observed in HPV positive OPSCC cases. Studies by Gillison et al and Yete S et al showed that prevalence of OPSCC is more in males and higher number of cases occur in tonsil(56-62%) followed by posterior third of tongue(40% cases). [12, 13]

Our study also showed similar results with 80% of cases in males and 44% cases in tonsil and 38% cases in posterior third of tongue. In particular HPV positive OPSCC were more common in tonsil (52.1%). Predilection to this site is explained by the fact that tonsil is the accessible lympho epithelial site for the virus[14,15] Statistically significant Lymphocytic immune response in tumors is also observed more in HPV associated tumors . Similar results also observed in many studies who explained that HPV positive tumors exhibit greater CD8 positive T cell infiltrate than HPV negative tumors. [16] Studies by Lewis et al showed that HPV associated tumors usually present in early stages (T1-2) with nonkeratinising morphology [17] whereas our study showed that most of the patients present in late stages but, most of the tumors were non-keratinizing. Worst pattern of invasion in oropharyngeal carcinomas is associated with poor outcome and early nodal metastasis. [18] We analysed the WPOI with HPV association. It showed that HPV positive tumors were associated with low WPOI which indirectly indicates that HPV positive tumors show better prognostic parameters in HPE. This is not statistically significant, this association needs analysis at large sample size. Many studies have also showed that HPV positive tumors are associated with better outcome.

Conclusion

HPV infection is of great concern nowadays because of its association with cancers especially cervix and oropharynx. These cancers behave well and have better prognosis irrespective of their differentiation. We analysed the histopathological parameters in HPV associated OPSCC and we found these tumors are most often nonkeratinising with rich lymphocytic immune response and low WPOI which are the good pathologic prognostic factors.

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